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ORIGINAL PAPER

Novel and versatile methodology for synthesis of β-aryl-β-mercapto ketone derivatives as potential urease inhibitors

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Abstract The objective was to obtain new scaffold of compounds possessing anti-urease activity. For this new and simple method for the synthesis of β-aryl-β-mercapto ketone derivatives based on Michael addition of thiophenol to chalcones in an ionic liquid as a solvent was improved. The products were obtained in good to moderate yields with high purity and characterized by spectral and elemental analyses. The activities of synthesized compounds were investigated as new inhibitors of jack bean urease. Among 22 synthesized compounds, all of them have shown inhibitory effect in micromolar range, and the most potent one has $IC_{50} = 6$ μM compared to hydroxyurea $IC_{50} = 100$ μM as a reference inhibitor. A docking study was performed using Autodock 4.2 in parallel to in vitro experiments to illustrate the corresponded binding affinities as well as binding site, and involved residues in interaction. These computational results complimented the experimental inhibition activity and enabled us to report a potent urease inhibitors based on β-aryl-β-mercapto ketone scaffold.

Keywords β-Aryl-β-mercapto ketone · Urease inhibitors · Molecular docking

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Introduction

The most widespread nickel metalloenzyme is urease (EC 3.5.1.5), which is an important enzyme in both agriculture and medicine [1, 2]. The two nickels were coordinated by His407, His409, Kcx490, His519, His545, and Asp633 in its active site [3]. It can hydrolyze urea which is an end product of the catabolism of nitrogen-containing compounds to form eventually ammonia and carbon dioxide [4].

Pathogenicity of *Helicobacter pylori* indicates that ammonia generated by urease on urea can cause injury to the gastroduodenal mucosa and helps bacteria to endure in the acidic pH of the stomach during colonization [5, 6]. Consequently, approaches based on specific inhibition of urease are the main treatment and eradication caused by this large heteropolymeric enzyme [7].

Recently, some complexes of Schiff bases showed a significant inhibitory activity against urease [8, 9]. In this regard, Chalcone derivatives have various therapeutic properties including antioncogenic [10], antiinflammatory [11], antitumor [12], antileishmanial [13], antifungal [14], and antiulcer [15] effects. Furthermore, it is reported that different enzymes inhibitors and antioxidants are designed based on chalcones [16–18]. Therefore, synthesis of such compounds is of great interest in view of variety of pharmacological properties. In the following, by undertaking a new procedure in synthesized saturated chalcons, β-aryl-β-mercapto ketones, we tried to explore novel inhibitors, which have better inhibition potency through urease. In recent years, inhibitors have been designed based on choosing the appropriate pharmacophoric groups [19–21]. Therefore, to obtain the precise three-dimensional structural information and better understanding of modes of interactions, a molecular docking study was performed and related pharmacophore was generated.

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Experimental works

Materials

TLC experiments were performed on pre-coated silica gel plates using EtOAc/hexane (1:4) as the eluent. Melting points were reported without correction. IR spectra were recorded using KBr disks on a Shimadzu IR Prestige-21 infrared spectrophotometer. ^{1}HNMR (125 MHz) and ^{13}C NMR (500 MHz) spectra were recorded on a FT-NMR Bruker Ultra Shield^{TM} as $CDCl_3$ solutions using TMS as internal standard reference. Mass spectra were obtained on a Fisons Trio 1000 instrument at ionization potential of 70 eV. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. Solvents and reagents were purchased from commercial sources. Different ionic liquids were prepared using known procedures [22, 23]. Also, the chalcone derivatives were prepared using Diels–Alder condensation. Known products were identical with authentic samples by melting points, TLC, and NMR determinations [24–35]. New product was characterized based on their ^{1}HNMR, ^{13}CNMR, IR, and mass spectra and their purity was confirmed by elemental analysis (supplementary data).

Chemistry

General and typical procedure synthesis of β-aryl-β-mercapto ketone derivatives

The general procedure is as follows: a mixture of [omim][Cl] (3 mmol, 0.7 gr), thiol **2** (1 mmol), chalcone derivative **12** (1 mmol), and water (0.5 ml) was stirred vigorously at room temperature. The reaction mixture was allowed to stir until the color changed from yellow to white (monitored by TLC and assisted by visual observation). The mixture was extracted with ethyl acetate (3 × 10 mL), and the combined ethyl acetate extract was washed with brine, dried (Na_2SO_4), and evaporated to leave the crude product. The crude product was purified by recrystallization in ethanol.

Biological assay

Jack bean urease (8 units/mg), phenol, and sodium nitroprusside were obtained from Sigma. Urea, sodium hydroxide, sodium dihydrogen phosphate, and sodium hydrogen phosphate were purchased from Merck and used without purification. All aqueous solutions were prepared in MilliQ water (Millipore, USA).

Total protein assay

For urease inhibition assays, after addition of 10 mL of phosphate buffer, in order to obtain the accurate concentration of the enzyme, sonication was performed for 60 s, followed by centrifugation and evaluation of the absorbance of upper solution in $\lambda = 280$ nm (Cecil-UV 9000) which is attributed to the enzyme. By using the following equation $A = \varepsilon bc$ where c is the concentration of solution (mol/L), b is the length of the UV cell, and ε represents molar absorptivity in the specific wavelength, we could calculate the concentration of initially urease solution. After proper dilution, the concentration of enzyme solution was 2 mg/ml.

Enzyme inhibition assay

Urease activity was determined by measuring the release of ammonia by a modification of the Berthelot reaction [36]. The reaction mixture contained 50 mM urea, 100 µl (2 mg/ml) of JBC, and 100 µl of the test compounds of various concentrations in 100 mM sodium phosphate buffer (pH 7.6). After pre-incubation for 30 min at 37 °C, the reaction was terminated by addition of 500 µl of 0.5 % phenol—0.0025 % sodium nitroprusside solution. Then, 500 µl of 0.25 % sodium hydroxide—0.21 % sodium hypochlorite solution was added, the mixture was incubated for 30 min at 37 °C for color development. This method is based on the released ammonia (NH_3) which reacts with hypochlorite (OCl^-) to form a monochloramine and the absorbance at 625 nm was determined. Urease activity of control was taken as 100 % and enzyme inhibition is expressed as % inhibition. All the results were of triplicate run.

Protocol of docking study

Computational resources

The computational studies were carried out on a computer cluster comprising four sets of HP Prolient ML370-G5 tower servers equipped with two quad-core Intel Xeon E5355 processors (2.66 GHz) and 4 GB of RAM, running a Linux platform (SUSE 10.2). Linux version of Molecular Graphics Laboratory Tools (MGLTools, 1.4.5), AutoDockTools (ADT), Autogrid4.2, and Autodock4.2 were downloaded from http://www.scripps.edu [37]. ADT was employed to set up the enzymes and ligands input files and viewing docking log files. Autogrid4.2 [37] and Autodock4.2 [37] were used to calculate grid box and docking experiments.

Protein preparation for docking

The crystal structure (3D structure) of urease enzyme with resolution of 2.05 Å was downloaded from the Brookhaeven protein data bank (3LA4, http://www.pdb.org) and was used for docking studies. In the present study, non-standard protein residues (KCX and CME) and the metal ions were

included in the binding site specification but before initiating the docking simulations, all other non-protein molecules (ligand and all water molecules) were removed from structure file [21, 38]. To prepare the urease structure for docking, polar hydrogen's, Kollman united atom charges, and solvation parameters were added using ADT and then kept rigid in the docking process, whereas all the torsional bonds of ligands were set free by Ligand module in ADT or using the *prepare_receptor4.py* script [37].

Ligand preparation for docking

All synthesized compounds (ligands) and thiourea were built by Marvin sketch applet (Marvin package, Chemaxon Company) and optimized using "Prepare Ligands" script in the ADT for docking studies. The ligand structures were prepared for docking by merging non-polar hydrogen atoms, adding Gasteiger partial charges, and defining rotatable bonds. The optimized ligand molecules were docked into urease model using Autodock4.2. The resulting docked poses with root mean square deviation values (RMSD) <2 Å were clustered together and the lowest energy minimized pose was used for further analysis. The best conformation of each of the ligand–urease complex was selected based on docking energy [37].

Docking parameters

In general, following parameters were used for docking simulations: the size of the docking grid was 40 × 40 × 40 Å points around active site of urease, The centre of the grid was set to the average coordinates of the two Ni^{2+} ions in the α chain of urease. The initial population size (*ga_pop_size*) was 150, and the maximum number of energy evaluations (*ga_num_evals*) was 25×10^6, maximum number of generations (*ga_num_generations*) was 27,000 and the number of Autodock Lamarckian genetic algorithm local search run jobs (*ga_run*) was 100. All other parameters were set to their default settings. On successful completion of docking, clustering analysis was performed and a conformation with the most favorable binding energy was selected. This protocol was then similarly applied to all synthesized compounds [21, 37, 38].

Results and discussion

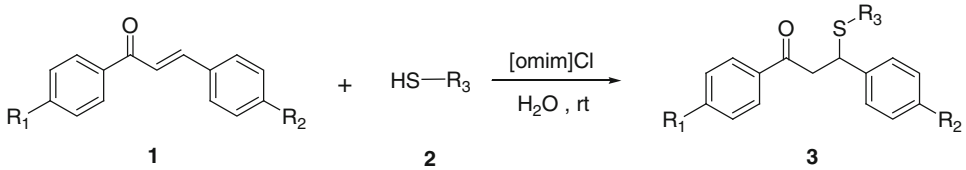
Chemistry

Each synthesis procedure has several drawbacks such as low yield, being time-consuming and using expensive catalysts. In the present work, we investigated the use of room temperature ionic liquids as catalytic and environmentally benign solvents for the facile homogenous synthesis of a series of substituted β-aryl-β-mercapto ketone without the use of any base or any special activation (Scheme 1). From the synthetic point of view, β-aryl-β-mercapto ketones are useful key steps in the synthesis of pharmaceutical compounds [39–43]. Therefore, the synthesis of β-aryl-β-mercapto ketone has attracted much attention in organic synthesis. In our continuing effort to evaluate these compounds inhibitory effect on urease, we were interested in utilizing ionic liquids as an environmentally attractive medium to develop new methodologies for the synthesis.

There are several reports in the literature for thia-Michael addition utilizing $ZrCl_4$–SiO_2 [44], $InCl_3$ [45], $Cu(BF_4)_2{\cdot}H_2O$ [46], $Zn(ClO_4)_2$ [47], and NaOH [48], hydrotalcites [49]. The Michael addition has attracted enormous attention as one of the most important sulfur–carbon bond forming reactions in organic synthesis [50]. These have generated interest to develop new methodologies for thia-Michael addition reaction for synthesis of some β-aryl-β-mercapto ketone derivatives. In order to substantiate the concept, all β-aryl-β-mercapto ketone derivatives studied were generated from 1,4-conjugate addition of a thiol to a chalcone derivatives via a thia-Michael addition in an ionic liquid at ambient temperature with an equimolar amounts of thiol and chalcone to afford the corresponding β-aryl-β-mercapto ketone derivatives (Table 1).

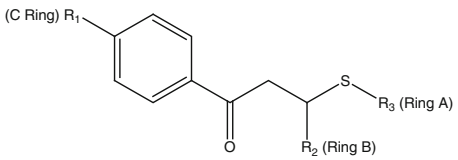
The reaction was optimized for preparation of 21 using 4-methoxychalcone with thiophenol in eight different ionic liquids, which were prepared in our laboratory (Table 2). Also, due to the high viscosity of some ionic liquids, a proper amount of water was added to control the mixing conditions. The results showed that the 1-octyl-3-methylimidazolium chloride [omim][Cl] would be the best ionic liquid for this reaction according to the obtained yield.

Scheme 1 Synthesis of series of substituted β-aryl-β-mercapto ketones



R_1 : H, Me, OH, R_2 : H, Cl, OMe, R_3 : Ph, Naphthyl, Octyl, 4-Cl-Phenyl, Benzyl, 2-AminoPhenyl, 2-Furylmethyl, 4-AminoPheny

Table 1 Structure and physical properties of β-aryl-β-mercapto ketones derivatives



Entry	R_1	R_2	R_3	Time (min)	Isolated yield (%)
1	H	4-Methyl-Phenyl	2-AminoPhenyl	15	91
2	4-Methoxy-Phenyl	4-Methoxy-Phenyl	2-AminoPhenyl	10	98
3	H	2-Nitro-Phenyl	2-AminoPhenyl	15	95
4	H	4-Cl-Phenyl	2-AminoPhenyl	5	95
5	H	Phenyl	2-AminoPhenyl	10	90
6	H	4-Methoxy-Phenyl	2-AminoPhenyl	25	90
7	H	4-Nitril-Phenyl	2-AminoPhenyl	30	90
8	H	Phenyl	4-AminoPhenyl	5	93
9	H	4-F-Phenyl	2-AminoPhenyl	5	91
10	OH	H	Phenyl	5	97
11	OH	H	Furane	15	94
12	H	Phenyl	Phenyl	5	97
13	H	Phenyl	Methyl-furan	15	93
14	H	Phenyl	Benzyl	8	63
15	H	4-Cl-Phenyl	Benzyl	6	97
16	H	Phenyl	Naphthyl	15	94
17	CH_3	Phenyl	Naphthyl	15	95
18	H	4-Methoxy-Phenyl	Benzyl	29	92
19	H	Phenyl	Octyl	25	90
20	H	4-Methoxy-Phenyl	4-Cl-Phenyl	20	90
21	H	4-Methoxy-Phenyl	Phenyl	25	90
22	H	4-Cl-Phenyl	Phenyl	5	95

Table 2 Different types of used ionic liquids in synthesized of compound 21

Entry	ILs	Time (min)	Yield (%)
1	[omim]BF_4	50	85
2	[bmim]BF_4	50	75
3	**[omim]Cl**	**50**	**95**
4	[omim]NO_3	50	93
5	[Hmim]I	50	60
6	[omim]$N(CN)_2$	50	55
7	[bmim]PF_6	50	50
8	[bpy]BF_4	50	60

Urease inhibition assays (in vitro)

The order of amino acids and their enzymatic mechanism in urease were preserved. So, in order to evaluate synthesized compounds inhibitory effects, biological experiments of all β-aryl-β-mercapto ketone derivatives were assessed against urease from jack bean which has >80 % similarity to *H. pylori* urease in its structure. Under the same condition, most of compounds showed potent urease inhibitory activities, compared with that of the standard inhibitor hydroxyurea, which had IC_{50} of 100 μM [51] as shown in Table 3.

According to Table 3, compound 3 shows the most potent inhibition through urease which is illustrated in Fig. 1. In this series, which consists of nine compounds (1–9), ring A contains amino group in different positions. As it illustrate shifting of amino group from ortho- (5, $IC_{50} = 56$ μM) to para- (8, $IC_{50} = 127$ μM) position deprive inhibitory effect since not only make some steric hindrance, but also NH_2 group places as far as Asn168 (5 Å) to make hydrogen binding in site of interaction. On the other hand, substituent of Cl and F group in ring B of 4 and 9, respectively, result in different activities. Compound 9 in comparison with 6 and 1 ($IC_{50} = 63$ and 28 μM, respectively) has $IC_{50} = 16$ μM. Moreover, it shows better affinity according to ΔG° values (-8.3 kcal mol^{-1}) to binding site when it has been

compared with 4 ($\Delta G^{\circ} = -7$ kcal mol^{-1}) (Table 3). This effect could be due to better stabilization of compound in site and closer interactions with His 274 and 138 residues. Besides, according to docking studies Met 366 positions in 3.4 Å of ring B that causes π–π interaction between sulfur atom of amino acid and ring. For investigation, other substituent on ring B different derivatives has been synthesized. Inserting electron with drawing nitro group in ortho-position of 3, result in binding free energy equal to −10.18 kcal mol^{-1} (Table 3). This effect partially diminishes in 2, which two electron donning methoxy groups have been inserted in para-position of rings B and C. Although this compound has bulkier groups, strong interaction of S and Met 366 has significant effect in its inhibition power. At last in this series, nitrile substitution in para-position of ring B as electron withdrawing group result 7 with $IC_{50} = 18$ μM that can be conclude, electron donning and withdrawing substituent on rings A and B, respectively, cause compounds with better inhibition which can be used as scaffold for next optimizations.

Table 3 Binding energy, final intermolecular, electrostatic energy from docking studies, and inhibitory activity of β-aryl-β-mercapto ketones derivatives against Jack bean urease

Compound	Binding energy (Kcal/mol)	Final intermolecular energy (Kcal/mol)	Electrostatic energy (Kcal/mol)	IC_{50} (μM)
1	−7.76	−8.15	−0.04	28
2	−8.48	−9.25	−0.32	12
3	−10.18	−11.60	−4.54	6
4	−7.00	−8.32	−0.08	102
5	−7.43	−9.16	−0.90	56
6	−7.02	−9.31	−1.40	63
7	−8.15	−8.94	−0.88	18
8	−6.90	−8.57	−0.75	127
9	−8.30	−8.98	−1.54	16.6
10	−7.59	−9.50	−1.80	35
11	−7.66	−8.77	−1.94	25
12	−7.02	−8.46	−0.74	85
13	−6.91	−8.56	−0.25	83
14	−6.90	−8.68	−0.37	151
15	−7.02	−8.82	−0.09	97
16	−7.98	−9.38	−0.67	16.3
17	−8.40	−9.81	−0.73	14
18	−6.73	−8.87	−0.08	167
19	−6.65	−8.78	−0.00	125
20	−7.20	−9.22	−1.76	71
21	−6.84	−8.81	−1.68	135
22	−6.57	−8.18	−0.68	181
Std	−5.39	−6.17	−0.73	100

Std hydroxyurea

In the next modification, hydroxyl group has been substituted in para-position of ring C. Urease inhibition has been increased in 10 ($IC_{50} = 35$ μM) in contrast with un-substitute one (12 with $IC_{50} = 5$ μM). Better inhibition by para-substitution of electron donning group previously has been approved in compound 2. In this group, ring A has been replaced by furan ring, 11. Juxtaposition of electron withdrawing group such as furan to sulfur atom of compounds, deplete charge on sulfur and result better hydrogen interaction. According to docking studies, 11 is entered to active site binding pocket through hydroxyl group similar to 10. For more insight to importance of nature of ring A and its distance to S atom, derivatives 13–18 have been synthesized. In all compounds, longer distances decrease inhibition potency, but this effect cover by inserting aromatic group, phenyl, instead of methyl as just hydrophobic group, 16 ($IC_{50} = 16$ μM) and 14 ($IC_{50} = 151$ μM), respectively. Indeed, enzyme inhibition was enhanced when the phenyl-carrying ligand was replaced by the naphthyl moiety. Observed inhibition may be due to the conformational change of urease by phenolics [52]. On the other hand, in 13 a phenyl ring has been replaced by furan in longer distance. This results in diminishing H-bond formation between thiol atom of 11 and near amino acids because of inappropriate placement in site. By the way, in

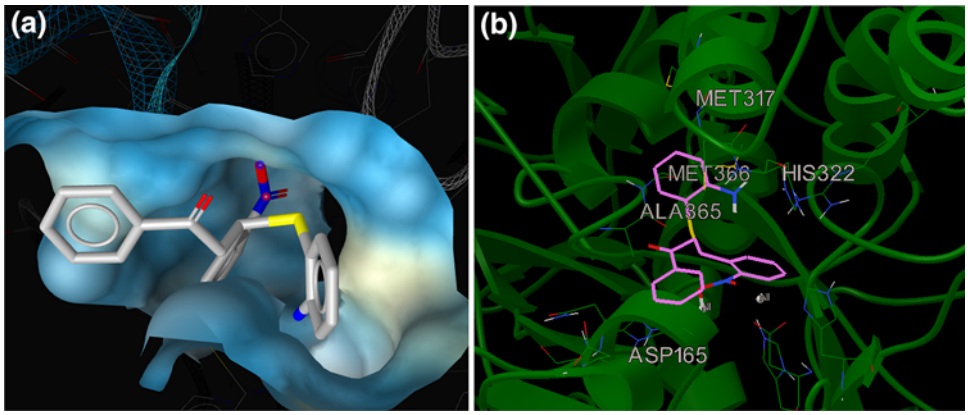


Fig. 1 Interaction diagram of the docked conformer of compound 3 with the active site residues of the enzyme. **a** Represented inhibitor perfectly fit into the enzyme active site. **b** Residues that are involved with interaction are demonstrated

13 hydrophobic interactions between additional methyl group and Ala169 partially improve potency In comparison with 14 with bulkier phenyl group, which causes steric hindrance. 17 in comparison with its relative structure, 16, demonstrate moderately improvement in inhibition potency due to additional hydrophobic interaction of methyl group in para-position and hydrophobic pocket that has been confirmed by docking studies. The bonding energy of earlier has been estimated -8.4 kcal mol^{-1}. Finally, effects of different substituent's have been studied by evaluate inhibition power of 15 and 18. Both compounds have penetrated to the entrance of urease active site from ring C, but 15 have penetrated more effectively and shows $\Delta G^{\circ} = -7.02$ kcal mol^{-1} (Table 3). This part could be more modified by chain groups, which make better diffusion of compound to active site without steric hindrance. This modification with lower efficiency is illustrate by evaluating inhibition potency of compound 19 which shows $IC_{50} = 125$ μM. Computational studies raveled that 19 ($\Delta G^{\circ} = -6.65$ kcal mol^{-1}) has been oriented trough active site from alkyl chain. Lower binding affinity of this compound may due to deleting aromatic ring A in contrast to 12 and 16. On the other hand, proper orientation of chlorine in 15 causes hydrophobic interaction with Ala 169 which has been missed in 18.

In the last series, compounds 20–22 were synthesized. Each type of substituent in para position of ring B (21 and 22 with $IC_{50} = 135$ and 181 μM, respectively) suppress inhibition effect which has been demonstrated earlier. However, in 20 with $IC_{50} = 71$ μM, hydrophobic interaction of chlorine group with residues stabilize compound tightly in the site apart of active site. All the interactions were analyzed by LigandScout 3.03b software and can be found in supplementary data.

This structure activity study on new scaffold of urease inhibitors is expected to provide rational information for the design of new potential inhibitors for urease. The studies on novel urease inhibitors are essential not only for the basic research on urease biochemistry, but also for the possible development of a highly needed therapy for urease-mediated bacterial infections.

Conclusion

We successfully developed an efficient, economical, and practical method for the synthesis of a series of β-aryl-β-mercapto ketone derivatives using inexpensive and readily available [omim]Cl under mild conditions without any acidic or basic catalysts. Synthesized compounds were evaluated for inhibition activity trough urease of jack bean. All of the compounds showed inhibitory properties through urease. In this series, compound **3** showed excellent inhibition among all. The binding pattern of this potential inhibitor which is localized in active site could help us to understand its inhibitory activity. Scaffold of β-aryl-β-mercapto ketone urease inhibitors can be utilized in further optimization to improve potency and selectivity by variations in the basic skeleton.

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